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The DEX/CRH test for major depression: A potentially useful diagnostic test

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ABSTRACT

The dexamethasone/corticotropin-releasing hormone (DEX/CRH) test has been proposed as a potential diagnostic test for major depressive disorder (MDD). A previously proposed four-step approach assesses the stage of development for a biological finding into a clinically useful diagnostic test. Using this approach, we evaluated the progress of the DEX/CRH test using meta-analysis as a part of step 1. A literature review identified 15 studies of the DEX/CRH test in patients with MDD and healthy controls. Meta-analysis estimated the effect size, heterogeneity, and confidence intervals using random effects models. Studies consistent with any step of the four-step approach were identified, and their characteristics were presented. Eleven studies reported significantly higher cortisol levels with the DEX/CRH test in patients with MDD, compared with the healthy controls (step 1). Eight eligible studies were included in meta-analysis, and had an effect size of 1.34 (95% confidence interval: 0.70–1.97). Most studies were step-1 studies (comparison of patients and healthy controls), and no step-4 studies (multicenter trials) were found. This review emphasizes that despite appearing as a promising test, the DEX/CRH has not been adequately studied for the required stages of development into a clinically useful laboratory test. Particularly, additional step-3 and step-4 studies are necessary.

1. Introduction

Among the efforts to utilize biological markers to establish ancillary laboratory tests to diagnose psychiatric disorders, one of the most popular and well-studied areas has been the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is known to play a critical role in mammalian stress responses, especially during chronic stress (Checkley, 1996; García et al., 2000). Alterations of this axis are postulated as key etiological factors in several psychiatric disorders, where dysregulations of the HPA axis are commonly observed (Ehlert et al., 2001; Simeon et al., 2007). This association is well defined in the case of HPA axis hyperactivity, which is believed to be the characteristic biological alteration found in a majority of patients with major depressive disorder (MDD) (Aubry et al., 2007). It is now more than four decades since the correlation between depression and HPA axis disinhibition was first demonstrated (Carroll et al., 1968; Carroll, 1982).

The most frequently utilized test to assess HPA system function in psychiatric disorders is the dexamethasone suppression test (DST) (Sher, 2006). The DST is performed by measuring cortisol levels following administration of a low dose of dexamethasone, normally suppressing cortisol through the negative feedback inhibition of the HPA axis. Impaired HPA function is expressed as non-suppression of cortisol following dexamethasone administration. The main mechanism of this alteration is hypothesized to be a down-regulation and reduced sensitivity of glucocorticoid receptors in the hippocampus and the cortex (Brooke et al., 1994; Modell et al., 1997; Pariante and Miller, 2001).

For several years, the DST was widely accepted among researchers and even clinicians, particularly for the distinction between the so-called "melancholic" from the "neurotic" types of depression (Carroll, 1982; Green and Kane, 1983). However, after a decade of popularity, extensive research cast doubt on the DST as a diagnostic procedure in psychiatry (APA Task Force on Laboratory Tests in Psychiatry, 1987; Nierenberg and Feinstein, 1988; Berger et al., 1988). Even a large cohort study in the Netherlands (Vreeburg et al., 2009b) concluded that individuals with current major depressive disorder were more likely to be cortisol suppressors.

The APA Task Force on Laboratory Tests in Psychiatry (1987) carried out an appraisal of the literature regarding the status of the DST in psychiatry. Methodological inconsistencies and interfering conditions were reported to contribute to the limited

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Table 1
Four-step approach (with permission, Arfken et al., 2009).

Step	Design	Purposes	Desired outcomes
1	Target group vs. healthy controls	1) Demonstration of significant deviance in the target group 2) Demonstration of test–retest reliability of finding	Provide evidence of a consistent biological abnormality in the target group
2	Target group vs. healthy and appropriate patient control groups	Demonstration of significant differential prevalence of abnormality between illnesses that frequently need to be differentiated from one another	Demonstration of potential clinical utility
3	Target vs. proper control groups (may include within target group sub-populations)	Definition of test-performance characteristics	Defining clinical utility
4	Same as in step-3 but across centers, ideally in a multicenter design	Demonstration and standardization of clinical application	Setting up standards for clinical application

sensitivity and specificity of the test. Nierenberg and Feinstein (1988) suggested that the DST had not undergone the standard evaluation process necessary for diagnostic tests. They reviewed 84 published articles and concluded that the DST had limited utility in differentiating depression from similar comorbid conditions, yielding a range of specificities far below the stated value. Other sources of misinterpretation were low reliability of assays measuring plasma cortisol and variable bioavailability of dexamethasone, which was corroborated by additional studies (Ritchie et al., 1990; Guthrie, 1991).

A multicenter World Health Organization (WHO) collaborative study (Gastpar et al., 1992) concluded that inconsistent methodologies and patient variables, such as sex and age, resulted in weak predictive power for describing symptom profiles among cortisol suppressors vs. non-suppressors. Several intervening conditions have also been identified to affect the DST, including weight loss, malnutrition, sleep, obesity, pregnancy, alcohol, infection, fever, dementia, diabetes mellitus, epilepsy, hypertension, and medications (Gaudiano et al., 2009). Another limitation of the DST was the pulsatile and circadian pattern of cortisol release, which was not reflected by the conventional test (Sherman et al., 1984; Deuschle et al., 1998).

Addressing the limitations of the DST, a modified version of the test was proposed in 1989, namely the dexamethasone/corticotropin-releasing-hormone (DEX/CRH) test, which examines the stimulating effects of CRH on ACTH (adrenocorticotropin hormone) and cortisol, under the suppressive action of dexamethasone (Bardeleben and Holsboer, 1989). Exogenously administered CRH normally overrides the dexamethasone suppression at the pituitary level, causing hypersecretion of ACTH and thereby cortisol. This effect is substantially enhanced in depressed patients, compared to control groups (Bardeleben and Holsboer, 1989; Holsboer-Trachsler et al., 1991; Kunugi et al., 2006). The mechanism is speculated to be an impaired signaling of glucocorticoid receptors, leading to increased endogenous CRH as well as arginine vasopressin (AVP), which is co-localized in the same hypothalamic neurons, and is demonstrated to synergize the effects of CRH at the pituitary level (Bardeleben and Holsboer, 1989; Ising et al., 2007). The DEX/CRH test is considered to be more closely associated with the HPA system than the standard DST (Deuschle et al., 1998).

The DEX/CRH test has also been studied in other psychiatric disorders. In manic patients, it revealed dysregulated HPA-system activity (Schmider et al., 1995). However, the degree of HPA-system dysfunction in schizophrenia patients seems to be less than in patients with affective disorders (Lammers et al., 1995).

Superior sensitivity of the DEX/CRH test compared with the regular DST has been confirmed (Ising et al., 2007; Watson et al., 2006). Conversely, it has modest specificity in differentiating different kinds of stressors (Oshima et al., 2001). Furthermore, depressed patients with chronic disease, those in outpatient settings, or those with atypical features did not show an increased response to the DEX/CRH test (Watson et al., 2002; Carpenter et al., 2009). Nevertheless, this test has been suggested to be a potential biomarker for treatment response in major depression in patients with an initially dysregulated HPA system (Ising et al., 2007).

Major depressive disorder (MDD) is a serious illness that will soon be the world's greatest public health burden, according to the World Health Organization (Boyle et al., 2005). However, no biological markers are available yet for inclusion in the diagnostic criteria of major depression (Mössner et al., 2007).

To systematically translate biological parameters into clinically useful diagnostic tests, we proposed a four-step approach (Boutros et al., 2005, 2008; Boutros and Arfken, 2007; Arfken et al., 2009), based on the previously published guidelines for deciding the clinical usefulness of diagnostic tests (Sackett, 1991) and the criteria of the Standards for Reporting of Diagnostic Accuracy (STARD) (Bruns, 2003; Bossuyt et al., 2003). The four-step approach was later further elaborated within each step (Arfken et al., 2009) to incorporate other guidelines, i.e. Appraisal of Guidelines for Research Evaluation (AGREE) (AGREE Collaboration, 2003) and evidence-based recommendations (Strauss, 2005). Characteristics of this step-wise approach are presented in Table 1. The current effort was undertaken to estimate the potential diagnostic value of the DST/CRH test. We categorized the published studies to date under our taxonomy and examined the effect size of the test in patients with MDD compared to health controls (step-1).

2. Methods

2.1. Inclusion and exclusion criteria

Studies with the objective of comparing the results of the DEX/CRH test in individuals with MDD and healthy control subjects or other patient groups, which also met the criteria of the four-step approach, were initially selected.

Studies not including a MDD group were excluded. Studies utilizing either sorely the DST or the CRH (not the combined test), studies measuring only baseline cortisol or ACTH (not in response to DEX/CRH), and studies probing a particular feature of depression (e.g. suicide) were also excluded. Review articles were not considered eligible for inclusion either. We also excluded the studies assessing the value of the DEX/CRH test only in treatment response (i.e. antidepressant efficacy or relapse prediction). While prediction of treatment response is undoubtedly a very important goal of laboratory testing, we elected to adopt this exclusion for two reasons. First the focus of the current review is on diagnosis. Secondly, our preliminary review of this literature suggested the number of reports using the exact same methodology (including testing prediction of response) was not adequate for a meaningful meta-analysis.

2.2. Literature search

The review of the literature on this topic was aimed at including all the published articles that could be identified as compatible with one or more of the four steps. PubMed was the database searched; PsychInfo yielded very few articles which were also available in PubMed. The search strategy was seeking articles